



Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Biostatistics

STATISTICAL REVIEW AND EVALUATION BLA

BLA/Supplement Number: 125419.0

Product Name: Influenza A (H5N1) Virus Monovalent Vaccine,
Adjuvanted

Indication(s): Active immunization for the prevention of disease in
persons 18 years of age and older at increased risk of
exposure to the influenza A virus H5N1 subtype contained
in the vaccine

Applicant: ID Biomedical Corporation of Quebec / GSK Biologicals

Date of Submission: February 22, 2012

Action Due Date: November 23, 2013

Review Priority: Standard

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1. EXECUTIVE SUMMARY

GSK submitted BLA 125419 to seek licensure of the AS-03 adjuvanted Influenza A (H5N1) Virus Monovalent Vaccine manufactured in Quebec (also referred to as Q-Pan H5N1.) This review focuses on the specifications and release requirements for Single Radial Immuno-Diffusion (SRID) assay used in potency testing of ---b(4)----- final container lots.

Because the stability data showed a potency loss over the proposed 36-month shelf life, GSK used an approach recommended in the WHO Guidelines on Stability Evaluation of Vaccines to calculate the minimum release specification. The approach is statistically acceptable for situations where degradation needs to be considered. This approach is different from the current CBER potency requirements for seasonal influenza vaccines and requires an expiry acceptance criterion (EAC) be specified. GSK defined EAC based on their statistical interpretation of the current CBER potency criteria for seasonal influenza vaccines. The EAC defined by GSK is not considered by the product reviewers to be what CBER's traditional potency acceptance criteria originally intended to mean.

Considering that the current CBER release requirements for seasonal influenza vaccines cannot be directly applied to the situation where there is potency loss over the shelf life, and the situation of a pandemic influenza vaccine is different from seasonal influenza vaccines, it is the statistical reviewer's opinion that the applicant's proposed potency release criteria are acceptable.

2. BACKGROUND

In the original submission, the specification of HA content by SRID test was set as “---b(4)-----” In the Information request (IR) dated July 30, 2012, CBER product reviewers requested a revision of the stability plan to align with CBER's policy on influenza vaccine policy (question 4):

4. In alignment with CBER's policy on influenza vaccines potency, we recommend that the mean HA content of the H5N1 drug product be within b(4) of the label claimed potency (i.e., ---b(4)-----HA/mL). To ensure that the actual potency threshold of the drug product shelf-life is met, the lower limit of the release specification should be not less than -b(4)-- HA/mL. Furthermore, the same criterion should be applied during the long term stability studies conducted in support of the shelf-life of the drug product. Please revise your stability plan to reflect this criterion.

In the August 16, 2012 teleconference, further comments were raised by Drs. Rajesh Gupta and Manju Joshi (DBSQC) regarding a difference between CBER's historical release requirements for the SRID potency test and GSK's proposed release requirements. On September 25, 2012, two additional questions regarding the SRID assay were sent to GSK:

1. For VR010 Radial Immunodiffusion for Low HA-concentration Influenza Vaccine- 9000018734-VO8, the SOP states, “---b(4)-----” Please clarify the following in your SOP:

2. For HA Content Summarized SOP 9000018772, the SOP states, "---b(4)-----"

In response to CBER's requests, GSK submitted Amendment 10 to provide responses and additional information. The applicant provided the statistical justification for the model used to calculate the release specification and the expiry acceptance criterion used in the calculation. Statistical evaluation of the applicant's responses was thus requested by the product reviewers.

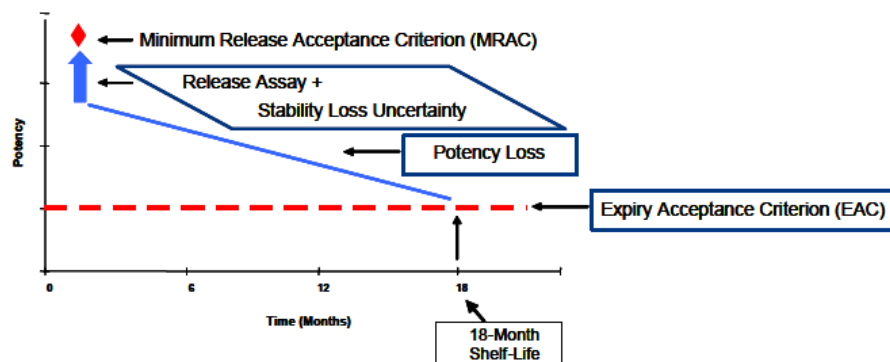
- CBER requirement: the measured potency not to be below b(4) of the intended potency (-b(4)-HA/mL) at release.
- The EP requirements: the lower bound of the 95% confidence interval on the measured potency must be -b(4)- of the intended potency (i.e. b(4) $\mu\text{g/mL}$ for a 15 $\mu\text{g/mL}$ pandemic antigen target) with a restriction on variability, expressed as the confidence interval, which cannot exceed -b(4)- of the measured content.

Based on the consideration of both CBER and EP requirements, a maximum relative variability of $\pm 10\%$ was proposed for product release. The statistical rationale is that for a mean potency of $\pm 100 \mu\text{g/mL}$, a $\pm 10\%$ maximum variability would give a lower 95% confidence limit of $90 \mu\text{g/mL}$. This variability criterion is more restrictive than the current CBER variability requirement of 12.3% for $n=3$ gels (10% for $n=6$ gels), and GSK believes it is achievable based on their experience with the assay $\pm 10\%$.

3

GSK used a statistical model, as outlined in the WHO Guidelines on Stability Evaluation of Vaccines, to calculate MRAC based on the decay rate estimated from stability evaluation and the EAC defined, taking the assay variability and uncertainty of stability loss estimation into consideration. The statistical model for MRAC calculation is illustrated in the following figure.

Figure 1 Illustration of Minimum Release Acceptance Criterion Determination



To calculate the MRAC using the statistical model described above, the EAC was set at $b(4) \mu\text{g/mL}$, which corresponds to the lower 95% confidence bound for the mean potency of $b(4) \mu\text{g/mL}$. The applicant justified the EAC by showing that with the current CBER release requirement (mean $-b(4)$ ----- SD $\geq 12.3\%$ for $n=3$ gels), the lower 95% bound is $b(4) \mu\text{g/mL}$, which is even lower than the proposed EAC of $b(4) \mu\text{g/mL}$.

The loss of potency over time is assumed to follow a first order, or exponential decay model (i.e., linear on the logarithmic transformed scale). The stability profiles of the $-b(4)$ ---- show a trend toward lower HA content over time (the loss rate is $-b(4)$ ----- ($\mu\text{g/mL}$)/month). The stability profiles of the final containers show that the HA content of the final containers is quite stable over time and that the position of the vials during storage has a limited impact on the stability (the loss rate is $-b(4)$ ----- ($\mu\text{g/mL}$)/month for the upright and inverted positions, respectively). The estimated loss between the actual titers of the final bulk and the target formulation is $-b(4)$ ----- ($\mu\text{g/mL}$).

Using the defined EAC and the estimated decay rates, uncertainty of the slopes and the assay variability from the stability analysis, the minimum release HA content was calculated by means of the following formula:

---- $b(4)$ -----

where:

- **MRAC** is the minimum release acceptance criterion
- **EAC (in the WHO formula)** is the 95% lower confidence bound (LCB) of the expiry acceptance criterion when this criteria is expressed as a mean value (i.e., 95% LCB is $b(4)$ for a mean value of $b(4)$ HA/mL and $b(4)$ standard deviation as proposed below).

- ----b(4)-----
- ----b(4)-----
- ----b(4)-----
- --b(4)-----
- -----b(4)-----

Justification of the Number of Assay Replicates

According to the applicant's testing plan, a minimum of 3 tests (usually b(4) tests) will be performed in order to avoid repeat testing. To justify the assay format, the applicant presented the calculated MRACs (shown in Table 1 below), using the proposed variability -b(4)- with either 3 or 6 gels, and CBER traditional potency requirements for influenza vaccines (i.e., b(4) of label claim with 12.3% variability on 3 gels and b(4) of label claim with 10% variability on 6 gels).

**Table 1 HA Content Minimum Release Titters for the Different Process Steps
(Process Capability of 0.55 and Confidence Level of 0.95)**

| |
|--|
| <div style="display: flex; align-items: center; justify-content: center;"> <div style="font-size: 4em; margin-right: 10px;">[</div> <div style="text-align: center;">b(4)</div> <div style="font-size: 4em; margin-left: 10px;">]</div> </div> |
|--|

The results showed that the assay format (3 or 6 gels) has a limited effect on the minimum release titers. A maximum difference of b(4) HA/mL is observed between both assay formats for -b(4)-- MRAC. The minimum release requirement calculated for all 6 replicates is less stringent than that for 3 replicates with the proposed -b(4)-- variability due to the tighter confidence resulting from a larger number of replicates. With the proposed variability of b(4) and -b(4)- MRAC of b(4) µg/mL, GSK considered it not necessary to increase the number of SRID replicates to six.

Reviewer's Comments:

CBER's traditional potency requirements for influenza vaccines and the applicant's approach are based on two different concepts for setting release specifications.

CBER's potency requirements (i.e., $b(4)\mu\text{g/mL}$ ($b(4)$ of label claim) with 12.3% variability on 3 gels and $b(4)\mu\text{g/mL}$ ($b(4)$ of label claim) with 10% variability on 6 gels) assume that the manufacturing process is in control, targeting at the label claimed $\geq 15 \mu\text{g/mL}$. The potency test for a vaccine lot to be released is just to check whether the observed potency is within the expected distribution of potency values with the maximum variability allowed. This expected distribution is narrower for the assay format of $n=6$ than for $n=3$, because of the higher precision achieved by having more replicates, making the criteria appear to be more stringent when the assay precision is better with more replicates. The requirements itself could not provide assurance that the true potency of a test lot is $\geq 15 \mu\text{g/mL}$, because the lower 95% confidence limit of a mean of $b(4) \mu\text{g/mL}$ could be as low as $b(4) \mu\text{g/mL}$. This means that a vaccine lot with true potency of $b(4) \mu\text{g/mL}$ may still have a chance to pass the release requirements and be released.

The applicant's approach, as described above, takes the decay rate, assay variability, and uncertainty of stability loss estimation into consideration in calculating the minimum release specification (MRAC) to ensure the potency of a vaccine lot remains above the stability specification (EAC). This approach requires that an EAC be defined. EAC is supposed to be the minimum acceptable potency for the vaccine.

While CBER's traditional potency requirements may be reasonable for manufacturing processes with established consistency and when no potency loss is expected over the desired length of shelf life, which is the case for seasonal influenza vaccine, it cannot provide a quantitative estimation of the minimum release specification when there is potency loss over the shelf life. Q-Pan H5N1 is intended to be stockpiled and the stability data showed a decay trend over the proposed 36-month shelf-life. The applicant's approach, recommended in the WHO Guidelines on Stability Evaluation of Vaccines, is acceptable in this situation. However, GSK set the EAC based on their statistical interpretation of the current CBER potency release requirements: the current CBER criteria imply that a potency of $b(4) \mu\text{g/mL}$ is the minimum acceptable potency. The EAC was thus set at $b(4) \mu\text{g/mL}$ in order to harmonize with the European requirements.

Based on discussions with Drs. Rajesh and Joshi of DBSQC, a stability specification of $b(4) \mu\text{g/mL}$ is not consistent with CBER's requirement for influenza vaccine potency. The following IR was sent to the applicant on November 9, 2012:

You used a statistical method, as described in the WHO document cited in the BLA, Amendment 10 (STN 125419/10), to estimate the minimum release acceptance criterion (MRAC), taking the loss of potency over the proposed shelf-life into consideration. You also interpreted CBER's current/historic influenza vaccine lot release requirements as implying that the lower 95% confidence limit of a mean of $b(4)\mu\text{g/mL}$, which is $b(4) \mu\text{g/mL}$, is an acceptable level of expiry acceptance criterion (EAC) for the calculation of MRAC. Nevertheless, you set your EAC at $b(4) \mu\text{g/mL}$ in order to align with the European requirement. Thus, you set the variability requirement at $b(4)$ such that the lower 95% confidence limit of a mean of $b(4)\mu\text{g/mL}$ would be $b(4)\mu\text{g/mL}$.

While the statistical method used for calculating your MRAC for $-b(4)$ -----final container is acceptable, we do not agree with your using $b(4) \mu\text{g/mL}$ as the EAC in the calculation of MRAC. The historic CBER influenza vaccine lot release requirements were set with the expectation that all

acceptable lots should contain at least the label claimed amount of antigen content, i.e. 15 ug/mL. The reportable potency value for a given lot (i.e., the mean of n values), however, can be lower than 15 ug/mL due to assay variability. The rationale behind the historic requirement is that the potency for a given lot should not be significantly lower than 15 ug/mL. For the assay format of 3 gels, a reportable potency value (mean of 3 values) of $b(4)$ ug/mL would be considered not notably lower than 15 ug/mL. For the assay format of 6 gels, due to the improved precision about the mean, a limit of $b(4)$ ug/mL is required to demonstrate that the potency is not notably lower than 15 ug/mL. Therefore, although CBER's lower release limit of $-b(4)$ ug/mL for the 3 gels or 6 gels format, set decades ago, can potentially be statistically interpreted in the way you interpret it, the CBER requirements do not intend to mean that CBER considers the lower 95% confidence limit of a mean of $b(4)$ (i.e. $b(4)$) an acceptable limit for the reportable potency value of a stability lot at the end of shelf-life. We consider a reportable potency value of $-b(4)$ ug/mL the stability limit (EAC) that should be used in your MRAC calculation. When the number of gels used is >3 (i.e., $-b(4)$ -----), the EAC to be used will be $-b(4)$ ug/mL

Please submit your revised MRACs for the final container and final bulk with detailed calculation information, including the formula and the values used in the formula.

In the teleconference on November 28, 2012, GSK presented slides and went over the history of the submissions, including CBER's advice given during the IND phase. GSK explained that their influenza vaccine manufacturing process has always been based on their interpretation of CBER's potency release requirements. If the expiry specification was set at $b(4)$ μ g/mL (i.e., $b(4)$ μ g/mL is considered as the lower 95% confidence bound for minimum acceptable potency), the impact on the vaccine production would be substantial (e.g., increase in HA content overage and manufacturing cost and decrease in HHS stockpile, manufacturing capacity, and process capability) and several of the clinical lots used in clinical studies which showed very good immunogenicity results would be out of specification at release by applying this stability potency requirement.

The review team discussed after the teleconference, and agreed that although there are some differences between GSK's proposal and CBER's traditional requirements for seasonal influenza vaccines, GSK's proposal is considered acceptable on the basis that this is a unique situation for the Q-Pan H5N1 pandemic vaccine (which contains an adjuvant and dose-sparing is highly desired during a pandemic) as compared to seasonal influenza vaccines and that the proposed release criteria will not impact CBER's long history for handling unadjuvanted inactivated seasonal influenza vaccines lot release.

Reviewer's Comments:

The EAC of $b(4)$ μ g/mL was used to calculate the MRAC for final bulk only, in order to assure that each lot will maintain potency above the EAC throughout labelled shelf-life. For the final container, the proposed release and stability acceptance criteria are still the same as the current CBER release criteria for 3 gels, except that a tighter standard deviation is required. Although GSK may have more than 3 tests for each reportable potency value (usually $b(4)$ tests -- the CBER criteria would then require a higher mean potency for $n>3$), with the tightened standard deviation requirement (CV $b(4)$) GSK's criteria can assure that the true potency is $\geq -b(4)$ -

$\mu\text{g/mL}$ while CBER criteria for $n=6$ (mean $\underline{-b(4)-}$ $\mu\text{g/mL}$ and $CV \leq 10\%$) can only provide assurance that the potency is $\underline{-b(4)-}$ $\mu\text{g/mL}$.

5. CONCLUSIONS

Considering that the current CBER release requirements for seasonal influenza vaccines cannot be directly applied to the situation where there is potency loss over the shelf life, and given the product reviewers' considerations on the unique situation of a pandemic influenza vaccine being different from seasonal influenza vaccines, it is the statistical reviewer's opinion that the applicant's proposed potency release criteria are acceptable.